Exploring the EBV-MS Link: A Mathematical Model of Immune Response Dynamics

Esha Manchanda

Department of Computer Science, Ashoka University

Multiple Sclerosis, a chronic autoimmune disorder affecting the central nervous system, has been increasingly associated with the Epstein-Barr Virus. This study presents an Ordinary Differential Equation model to explore this connection, particularly focusing on the immune response dynamics to EBV and its implications in MS. The model simulates the interaction between EBV infection and the immune system, proposing a mechanism whereby T-cell exhaustion leads to uncontrolled lytic activity of EBV in B cells. This process results in chronic inflammation, a key characteristic of autoimmune diseases, including MS. The model's preliminary predictions align with observed clinical data, suggesting a way in which EBV infection could contribute to MS pathogenesis.

0 INTRODUCTION

0.1 Multiple Sclerosis

Multiple Sclerosis is a chronic autoimmune disorder that primarily affects the central nervous system, leading to a wide range of neurological symptoms. It is characterised by the immune system's attack on the protective covering of neurons, the myelin sheath. This attack results in communication disruptions between the brain and the rest of the body, manifesting in symptoms such as fatigue, mobility issues, pain, cognitive impairment, and visual disturbances.

The exact cause of MS remains unknown textbf– current theories suggest a combination of genetic susceptibility and environmental factors that contribute to its development. However, several critical questions remain unsolved in MS research. These include the precise mechanisms driving its onset and progression, why some individuals develop MS while others do not, and the variability in the severity and course of the disease among patients. .

0.2 Epstein-Barr Virus

Epstein-Barr Virus, a member of the herpesvirus family, is one of the most common human viruses globally. It is estimated that EBV infects about 95% of adults worldwide, typically acquired during childhood or early adulthood. The virus has the unique ability to establish a lifelong latent infection in the host's B cells. During latency, the virus remains dormant with minimal expression of its genes, allowing it to evade the immune system's surveillance.

Primary EBV infection can manifest as infectious mononucleosis in some individuals, especially when the infection occurs during adolescence or young adulthood. Symptoms of infectious mononucleosis include fever, sore throat, swollen lymph nodes, and fatigue. Most EBV infections, however, are asymptomatic.

Beyond mononucleosis, EBV has been associated with several other diseases. It is a known risk factor for certain types of cancers, such as Hodgkin's lymphoma, Burkitt's lymphoma and Nasopharyngeal Carcinoma. [1].

0.3 EBV Association in MS

Several studies have indicated that MS is a rare complication of EBV infection. A longitudinal study of over 10 million US military personnel demonstrated that the risk of MS is minimal in individuals not infected with EBV and increases 32-fold following EBV infection. Moreover, studies have identified heightened immune responses to EBV within the CNS of individuals with MS. A critical marker of this response is the presence of EBV-reactive oligoclonal bands in the cerebrospinal fluid. Oligoclonal bands are proteins that indicate an immune response within the CNS. The reactivity to EBV in these bands suggests that the immune system in MS patients is actively responding to EBV-related antigens within the CNS. Another aspect of the immune response in MS patients is the presence of antibodies in their blood that bind to EBV proteins, such as the EBV Nuclear Antigen 1(EBNA1) in the brain. This binding pattern is indicative

of an abnormal immune response to EBV in MS patients, further linking the virus to the pathogenesis of the disease. Further evidence comes from the observed cross-reactivity of antibodies. In people with MS, antibodies that are formed against EBV antigens have been found to also react with self-antigens in the body. This cross-reactivity implies that the immune response to EBV may attack the body's own myelin sheath. Lastly, the success of B cell depletion therapies in treating MS underscores the role of B cells, and by extension, EBV, in the disease's progression. [2]

In healthy individuals, EBV lytic cycle reactivation is a common and often asymptomatic process. CD8+ T cells effectively regulate this reactivation, maintaining a balance that prevents disease manifestation. However, aberrant lytic activity of the virus is linked with MS. Despite the presence of an increased number of EBV-specific CD8+ T cells in MS patients — ostensibly a sign of a robust immune response — these cells demonstrate an impaired functionality. This suggests a state of 'exhaustion' in these immune cells. This exhaustion, characterised by reduced cytokine polyfunctionality, might be a factor in the inadequate control of EBV reactivation, allowing for the accumulation of EBV-infected autoreactive B cells in the brain. These B cells, especially during phases of active disease, exhibit increased lytic gene expression, suggesting a dysregulated EBV latency. [3] [4]

Therefore, this study posits that the exhaustion of CD8+ T cells leads to an increased rate of lytic EBV reactivation in MS patient B cells. It aims to model and analyse the dynamics between the functional status of CD8+ T cells and the activity of lytically infected EBV cells. Specifically, it aims to delineate how varying degrees of T cell exhaustion influence the reactivation rate of EBV and its subsequent impact on MS progression.

1 Methodology

1.1 Model Overview

This project presents an adapted mathematical model based on the framework established by Giao T. Huynh [5] , to investigate the within-host dynamics of Epstein-Barr Virus infection, with a focus on the implications for multiple sclerosis.

The model captures the progression and control of EBV through a network of interactions involving B cells in various states (naive, latently infected, memory, and lytically infected), uninfected and lytically infected epithelial cells, and cytotoxic T lymphocytes divided into two groups targeting latently infected B cells and lytically infected cells, respectively.

The model's framework is constructed upon a system of eleven ordinary differential equations, each representing the evolution of the population of cells or viruses over time. These equations account for the rates of infection, proliferation, and death of cells, as well as the production and clearance of viruses. Cytotoxic T lymphocytes are modeled to undergo activation and proliferation in response to EBV antigens, with their dynamics governed by saturating functions reflective of the biological limitations on activation and proliferation.

By extending the model from Giao T. Huynh, I aim to characterize the trajectory of EBV infection and explore how CTL exhaustion could potentially modulate EBV reactivation rates, thereby influencing MS progression.

1.2 Model Compartments

1. B Cells
   a. B1 (Naive B cells): Represent the susceptible B cell population that can be infected by EBV.
   b. B2 (Latently Infected B cells): These are B cells that have been infected by EBV and harbour the virus latently. They can proliferate and are subject to attack by cytotoxic T lymphocytes (CTLs).
   c. B3 (Latently Infected Memory B cells): These are latently infected B cells that have differentiated into memory cells. They are not recognized by CTLs and maintain a certain level of homeostasis in the immune system.
   d. B4 (Lytically Infected B cells): These B cells are actively producing new viruses, leading to the lysis of the cell. They can also be killed by CTLs.

2. Epithelial Cells
   a. E1 (Uninfected Epithelial cells): These are the healthy epithelial cells that can be infected by EBV.
   b. E4 (Lytically Infected Epithelial cells): These are epithelial cells that are actively producing new viruses and can be lysed as a result.

3. Virus Particles
   a. VB (B cell-derived virus): Virus particles that have been produced by B cells.
   b. VE (Epithelial cell-derived virus): Virus particles that have been produced by epithelial cells.

4. Cytotoxic T Lymphocytes (CTLs)
   a. T2 (CTLs against B2 cells): CTLs that target latently
   b. infected B cells (B2). T4 (CTLs against B4 and E4 cells): CTLs that target lytically infected B cells (B4) and epithelial cells (E4).

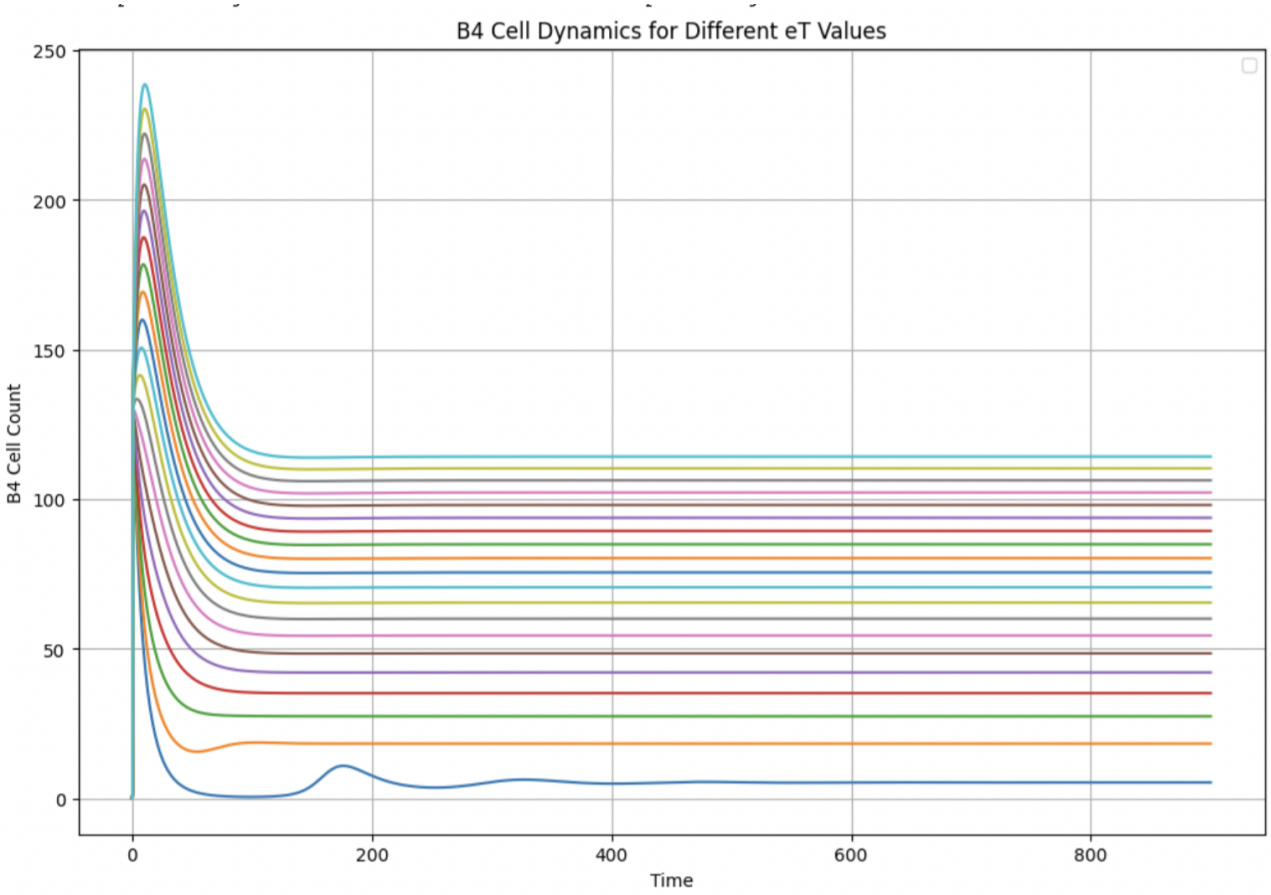

Fig. 1. B cell dynamics for varying rates of T cell exhaustion.

1.3 Model Equations

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\begin{aligned}
\frac{dB_1}{dt} &= d_1(B_0 - B_1) - \mu_{EB}V_{EB}B_1 - \mu_{VB}V_B B_1 \\
\frac{dB_2}{dt} &= \rho(\mu_{EB}V_{EB}B_1 + \mu_{VB}V_B B_1) - (d_2 + c)B_2 - k_2 B_2 T_2 \\
\frac{dB_3}{dt} &= cB_2 + rB_3 - srB_3 \\
\frac{dB_4}{dt} &= rB_3 - d_4 B_4 - k_4 B_4 T_4 \\
\frac{dE_1}{dt} &= d_e(E_0 - E_1) - \mu_{EB}V_{EB}E_1 - \mu_{VE}V_E E_1 \\
\frac{dE_4}{dt} &= \mu_{EB}V_{EB}E_1 + \mu_{VE}V_E E_1 - (d_e + \gamma)E_4 - k_4 E_4 T_4 \\
\frac{dV_B}{dt} &= nd_4 B_4 - d_v V_B \\
\frac{dV_E}{dt} &= n\gamma E_4 - d_v V_E \\
\frac{dT_2}{dt} &= \phi_2 T_1 w(B_2) + \theta_2 T_2 w(B_2) - \delta T_2 \\
\frac{dT_4}{dt} &= \phi_4 T_1 w(B_4 + E_4) + \theta_4 T_4 w(B_4 + E_4) - \delta T_4 - eT4 \\
\frac{dT_{4exh}}{dt} &= eT4 - \delta_{exh} T_{4exh}
\end{aligned}
$$

$\frac{dB_1}{dt}$:describes the rate of change over time of naive B cells B_1. (1)

- $d_1(B_0 - B_1)$: This term represents the recruitment of new naive B cells. B_0 is the source or initial population of naive B cells, and d_1 is the rate at which naive B cells are supplied from this source. This term assumes that the production of naive B cells is a regulated process that tries to maintain the number of naive B cells at a certain level B_0. If B_1 is less than B_0, this term is positive, indicating that new naive B cells are being produced. If B_1 is equal to B_0, no new naive B cells are produced.
- $\mu_{EB}V_{EB}B_1$: This term represents the loss of naive B cells due to infection by the epithelial-cell-derived virus V_{EB}. μ_{EB} is the rate at which the epithelial-cell-derived virus infects naive B cells. As the product $V_{EB}B_1$ increases, more naive B cells are lost to infection, leading to a decrease in the B_1 population.
- $\mu_{BB}V_{BB}B_1$: Similarly, this term represents the loss of naive B cells due to infection by the B-cell-derived virus V_B. μ_{BB} is the infection rate of the B-cell-derived virus. Again, as the product $V_{BB}B_1$ increases, more naive B cells are lost to infection.

$$\frac{dB_2}{dt} \text{:describes the rate of change over time of latently infected B cells } B_2. \quad (2)$$

- $\rho(\mu_{EB}V_{EB}B_1 + \mu_{BB}V_{BB}B_1)$: This term accounts for the production of latently infected B cells. The infection of naive B cells B_1 by both epithelial-cell-derived virus V_{EB} and B-cell-derived virus V_B contributes to this. The parameters μ_{EB} and μ_{BB} represent the infection rates by the respective viruses, and ρ is the proliferation factor that converts the infected naive B cells into the latently infected B cells B_2.
- $(d_2 + c)B_2$: This term represents the loss of latently infected B cells through natural death or transition to another state. d_2 is the rate at which these cells die naturally, and c is the rate at which latently infected B cells transition to the memory state B_3 due to the EBV gene expression switching off.
- $k_2B_2T_2$: This term captures the immune response against latently infected B cells. T_2 are the cytotoxic T lymphocytes that target latently infected B cells B_2. The constant k_2 is the rate at which these immune cells kill the latently infected B cells.

$$\frac{dB_3}{dt} \text{ : describes the rate of change over time of Latently Infected Memory B cells } B_3. \quad (3)$$

- cB_2: This term represents the rate at which latently infected B cells B_2 switch to the memory cell state B_3. The parameter c is the rate of this conversion process. It indicates that a certain proportion of the B_2 cells will become memory cells, thus increasing the B_3 population.
- rB_3: This term accounts for the proliferation or growth of the existing memory B cell population. The parameter r is the rate at which memory B cells divide. This term contributes to the increase of B_3 cells as they replicate.
- srB_3: This term represents the homeostatic death of memory B cells. In the context of the model, s is the homeostatic regulation factor, which controls the size of the memory B cell population. The product srB_3 thus gives the rate at which memory B cells are lost due to homeostatic mechanisms that keep the population in check.

$$\frac{dB_4}{dt} \text{ : describes the rate of change over time of lytically infected B cells } B_4. \quad (4)$$

- rB_3: This term indicates the rate at which memory B cells B_3 become lytically infected, thereby transitioning into plasma cells B_4. The parameter r here represents the rate of reactivation of the virus from the latently infected memory B cells to the lytic phase, which is when the virus begins to actively replicate and produce new viral particles, converting memory B cells into plasma cells.
- d_4B_4: This term accounts for the natural death rate of the plasma cells B_4. The parameter d_4 is the rate at which these cells die off naturally, which reduces the B_4 population.
- $k_4B_4T_4$: This term describes the killing of lytically infected B cells B_4 by the cytotoxic T lymphocytes that specifically target these infected cells T_4. The constant k_4 is the rate at which this immune-mediated killing occurs, which also decreases the B_4 population.

$$\frac{dV_E}{dt} \text{ : describes the rate of change over time of B-cell-derived virus .} \quad (5)$$

- nd_4B_4: This term represents the production of new virus particles by the lytically infected B cells B_4. Here, n stands for the average burst size, or the number of new viruses produced per lytically infected B cell when it bursts. The parameter d_4 is the rate at which these cells die and release new virus particles. So, the product nd_4B_4 gives the rate of new virus production.
- d_vV_B: This term accounts for the loss of B-cell-derived virus particles due to natural decay or clearance by the immune system. The parameter d_v is the decay rate of the virus, representing how quickly the virus particles are removed from circulation.

$$\frac{dV_E}{dt} \text{ : describes the rate of change over time of epithelial-cell-derived virus.} \quad (6)$$

- $n\gamma E_4$: This term represents the production of new V_E viruses from lytically infected epithelial cells E_4. The rate at which these cells release new viruses is denoted by γ, so the product $n\gamma E_4$ gives the total rate of virus production.
- d_vV_E: This term accounts for the natural decay or clearance of the virus (V_E) from the system. The parameter d_v is the rate at which the virus is cleared or dies out.

$$\frac{dE_1}{dt} \text{ : describes the rate of change over time of uninfected epithelial cells within the host.} \quad (7)$$

- $d_e(E_0 - E_1)$: This term represents the turnover of uninfected epithelial cells. d_e is the turnover rate, E_0 is the initial population of uninfected epithelial cells, and E_1 is the current population of uninfected epithelial cells. This difference $E_0 - E_1$ indicates that the population of uninfected cells will increase or decrease towards a homeostatic level E_0 at a rate determined by d_e.

- $\mu_{EB}V_B E_1$: This term represents the rate at which uninfected epithelial cells E_1 become infected by the B-cell-derived virus V_B. μ_{EB} is the infection rate by V_B, indicating that a higher viral load or a higher number of susceptible cells will result in more infections.
- $\mu_{EV}V_E E_1$: This represents the rate at which uninfected epithelial cells E_1 become infected by the epithelial-cell-derived virus V_E. μ_{EV} is the infection rate by V_E, and it also implies that more infections occur with a higher viral load or more susceptible cells.

$\frac{dE_4}{dt}$: describes the rate of change over time of lytically infected epithelial cells within the host. (8)

- $\mu_{BE}V_E E_1$: This term represents the rate at which uninfected epithelial cells E_1 become lytically infected due to the epithelial-cell-derived virus V_E. The μ_{BE} is the infection rate constant, dictating how quickly the infection spreads from the virus to the epithelial cell.
- $\mu_{EE}E_1$: This term is the rate of lytic infection of epithelial cells by the virus V_E, with μ_{EE} being the specific infection rate constant.
- $(d_e + \gamma)E_4$: This term accounts for the natural death rate d_e of the lytically infected epithelial cells and their death due to virus bursting out γ.
- $k_4 E_4 T_4$: This represents the rate at which lytically infected epithelial cells E_4 are killed by the effector T cells T_4. The constant k_4 is the rate of immune-mediated killing.

$\frac{dT_2}{dt}$: describes the rate of change over time of effector cytotoxic T cells targeting latently infected B cells (9)

- $\phi_2 \tau_1 w(B_2)$: This term represents the activation of naive CTLs T_1 into effector CTLs T_2 that target latently infected B cells. ϕ_2 is the rate at which this activation happens when stimulated by viral antigens from latently infected cells, τ_1 is the total naive CTL population, and $w(B_2)$ is a saturating function that depends on the number of latently infected B cells B_2.
- $\theta_2 \tau_2 w(B_2)$: This term denotes the proliferation of already activated CTLs T_2. θ_2 is the rate at which the effector cells proliferate upon stimulation by viral antigens from latently infected cells, τ_2 represents the effector CTL population, and $w(B_2)$ again is the saturating function of the infected cell population.
- δT_2: This represents the death rate of the effector CTLs (T_2), with δ being the constant death rate.

$\frac{dT_4}{dt}$: describes the rate of change over time of effector cytotoxic T cells targeting lytically infected B cells. (10)

- $\phi_4 \tau_1 w(B_4 + E_4)$: This term represents the activation of naive CTLs into effector CTLs that target lytically infected cells T_4. ϕ_4 is the activation rate, τ_1 is the naive CTL population, and $w(B_4 + E_4)$ is the saturating function dependent on the number of lytically infected B cells B_4 and epithelial cells E_4.
- $\theta_4 \tau_4 w(B_4 + E_4)$: This term represents the proliferation of activated effector CTLs T_4 in response to lytically infected cells. θ_4 is the proliferation rate, τ_4 is the effector CTL population, and $w(B_4 + E_4)$ is the saturating function of the infected cell population.
- δT_4: This is the death rate of the effector CTLs (T_4), with δ as the constant death rate.

$w(B_j) = \frac{B_j}{K + B_j}$: describes saturating function for T cells. (11)

- Ensures that the activation and proliferation of CTLs cannot increase indefinitely and will plateau as the number of infected cells increases, where K is the number of infected cells at which the CTL activation or proliferation is half maximal.

$\frac{dT_{4\text{exh}}}{dt}$: describes the exhaustion of effector T cells targeting lytically infected B cells. (12)

- $e_{T_4} T_4$ This is the rate at which T_4 cells become exhausted, with e_{T_4} as the constant exhaustion rate.
- $\delta_{exh} T_{4exh}$ This is the death rate of the effector CTLs T_4, with δ_{exh} as the constant death rate.

1.4 Model Assumptions

- The production and death of free viruses are modeled using linear terms, which may not fully capture the nonlinear dynamics of viral replication and clearance.
- B cells are naive and equally susceptible to EBV infection. This simplification overlooks the fact that EBV primarily targets B cells expressing CD21 receptors, whose presence varies among individuals and B cell subtypes. Additionally, different B cell subtypes exhibit varying susceptibility to EBV, influenced by their differentiation stage.
- CD8+ cells, once exhausted, lose all functional capacity to combat EBV infection.
- Rates of infection, cell turnover, proliferation and death to be constants with time.

Table 1. Parameters values

Parameter	Description	Value	Unit
d_1	Turnover rate of naive B cells	$1/6000$	min^{-1}
μ_{Eb}	B cell infection rate per epithelial-cell virus	3.3×10^{-10}	$\text{min}^{-1}\text{virus}^{-1}$
μ_{Bb}	B cell infection rate per B-cell virus	$\mu_{Eb}/100$	$\text{min}^{-1}\text{virus}^{-1}$
ρ	Proliferation factor	2	(no unit)
d_2	Death rate of latently infected B cells	$1/11520$	min^{-1}
c	Rate of latently infected cells going into memory stage	0.001	min^{-1}
k_2	Rate of latently infected B cells killed by T cells	3.8×10^{-8}	$\text{min}^{-1}\text{cell}^{-1}$
r	Rate of reactivation of lytic infection from latent infection	8.3×10^{-5}	min^{-1}
s	Regulation factor of memory B cells	2	(no unit)
d_4	Death rate of lytically infected cells due to viruses bursting out	$1/4320$	min^{-1}
k_4	Rate of lytically infected B cells killed by T cells	7.6×10^{-8}	$\text{min}^{-1}\text{cell}^{-1}$
d_e	Turn-over rate of epithelial cells	$1/6000$	min^{-1}
μ_{Be}	Epithelial cell infection rate per B-cell virus	3×10^{-11}	$\text{min}^{-1}\text{virus}^{-1}$
μ_{Ee}	Epithelial cell infection rate per epithelial-cell virus	$\mu_{Be}/5$	$\text{min}^{-1}\text{virus}^{-1}$
γ	Death rate of infected epithelial cells due to viruses bursting out	$1/6000$	min^{-1}
n	Viral burst size	1000	virus-cell^{-1}
d_v	Death rate of virus	$1/2160$	min^{-1}
ϕ_2	Rate of T cell activation against latent infection	1.95×10^{-5}	min^{-1}
ϕ_4	Rate of T cell activation against lytic infection	4.48×10^{-5}	min^{-1}
θ_2	Rate of T cell proliferation against latent infection	3.25×10^{-5}	min^{-1}
θ_4	Rate of T cell proliferation against lytic infection	3.25×10^{-5}	min^{-1}
K	Number of infected cells when T cell activation is half maximal	10^5	cell
δ	Death rate of T cells	$1/156000$	min^{-1}

- All interactions between cells and viruses are equally likely, spatial organization of tissues and compartments within the host are ignored.
- Only the role of cytotoxic T lymphocytes has been considered in eliminating EBV infection.

2 Preliminary Results

Under no T cell exhaustion, the model demonstrates a rapid decline in the population of lytically infected B cells, aligning with the immune response typically observed. Within a few weeks, the levels of these cells diminish almost to zero, indicative of a functional immune system's capability to control EBV reactivation.

However, the response changes markedly in the presence of T cell exhaustion. The model illustrates that when the functionality of T cells is compromised, there's a stabilisation of lytically infected B cells at significantly higher levels. This stabilisation does not revert to the minimal levels observed in healthy individuals, suggesting a persistent and uncontrolled viral activity.

A key observation from the model is the direct correlation between the rate of T cell exhaustion and the increase in lytically infected B cells. As T cell functionality diminishes, the number of these infected cells escalates, underscoring the critical role of T cell exhaustion in the disease process.

The stabilisation of lytically infected B cells at high levels in the context of T cell exhaustion provides a plausible pathway to chronic inflammation. This persistent viral activity could foster an environment conducive to molecular mimicry, where immune responses against EBV may inadvertently target similar antigens on the myelin sheath, triggering MS.

3 Future Work

My thesis will aim to analyse the stability of equilibrium points and explore how changes in parameters, such as the rate of T-cell response or viral replication, can lead to different system behaviours. Understanding the conditions under which the system shifts from a stable to an unstable state will provide insights into the potential triggers of MS exacerbations in the presence of EBV.

Furthermore, the study will involve conducting sensitivity analysis and parametric studies to explore threshold values of critical parameters, such as the rate of viral replication (r), that lead to a shift in the system's behaviour. This analysis is crucial in understanding the precise conditions under which EBV infection transitions from a

latent to an active state, contributing to MS pathogenesis.

Additionally, the research will include varying parameters related to T cell function, such as activation rate, exhaustion level, and response efficacy. This approach aims to provide deeper insights into the immune mechanisms at play in the context of the EBV-MS system.

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